REMARKS

Claims 26-49, 56-65 and 71-93 are pending.

Claims 26-28, 30, 31, 34-36, 37-39, 42-44, 45, 46, 49, 56-59, 61-64 and 71-74 have been amended to recite that the SNRI is a NE > 5-HT SNRI. Claims 26, 35, 43, 56, 61 and 71 have been amended to recite that the NE > 5-HT SNRI has a NE > 5-HT ratio of inhibition of about 2:1 to about 10:1. Support for the claim amendments can be found in the specification at page 7, lines 7-8.

Applicant notes that claims 76-93, directed to methods for administering milnacipran, are included in the provisional double patenting rejection, but are not otherwise accounted for in the Office Action. Applicant has included arguments for the patentability of claims 76-93 in the following remarks.

I. The rejection of claims 26, 28, 29, 32, 33, 35, 39-41, 43, 47, 48, 56, 58, 60, 61, 63, 65, 66, 70, 71, 73, and 75 under 35 U.S.C. § 102(b)

Claims 26, 28, 29, 32, 33, 35, 39-41, 43, 47, 48, 56, 58, 60, 61, 63, 65, 66, 70, 71, 73, and 75 have been rejected under 35 U.S.C. § 102(b) as anticipated by WO 00/32178 ("'178"). The Examiner contends that '178 discloses "a method of using a SNRI to treat pain of CFS and FMS using sibutramine" (Office Action, page 2). Further, the examiner contends that a compound that yields the instant method inherently has NMDA receptor antagonist properties (*id.*). The examiner was not persuaded by Applicant's previous argument that the instant claims are not anticipated by '178 because this reference discloses a compound (i.e., sibutramine) that is a triple reuptake inhibitor and not a SNRI. According to the examiner, a SNRI inherently "also inhibits the reuptake of dopamine" because a SNRI "yields the method" of '178 (*id.*).

A. A SNRI does not inherently inhibit the reuptake of dopamine

Applicant respectfully submits that, contrary to the Examiner, a SNRI does not inherently inhibit the reuptake of dopamine. As Dr. K. Ranga Rama Krishnan, Chairman of Psychiatry at Duke Medical Center and an expert in psychiatric pharmacology, states in his attached Declaration, a SNRI compound is distinct from a triple reuptake inhibitor compound such as

sibutramine (Declaration of Dr. K. Ranga Rama Krishnan under 37 C.F.R. § 1.132, paragraph 12) ("Krishnan Declaration") (attached as Exhibit 1). According to Dr. Krishnan, a SNRI compound does not inhibit the reuptake of dopamine. *Id.* Thus, the reuptake of dopamine is not an inherent feature of a SNRI.

B. A compound that yields the instant method does not inherently possess NMDA receptor antagonist properties

NMDA receptor antagonism is not an inherent feature of a compound that yields the instant method because: (1) the claimed methods are directed to the treatment of FMS, CFS, and pain, (2) the specification discloses that venlaxafine and duloxetine have been reported to be effective for the treatment of pain, CFS and FMS (specification, page 10, lines 16-20), and (3) at least one compound that yields the instant method, i.e., duloxetine, does not posses NMDA receptor antagonistic properties. *See* the poster entitled "Monoamine Reuptake and NMDA Antagonist Profile of Milnacipran: A Comparison to Duloxetine," presented by S. Rao at the 32nd Annual Meeting of the Society for Neuroscience in Orlando, Florida on November 7, 2002 (attached as Exhibit 2) ("the Poster"). Thus, NMDA receptor antagonism is not inherent in a SNRI compound because at least one SNRI (duloxetine) does not have this property. Accordingly, NMDA receptor antagonism is not an inherent property of a compound that yields the instant methods.

Claims 76-93 are directed to a specific SNRI, i.e., milnacipran, which has NMDA receptor antagonist properties (specification, page 9, lines 25-26). Claims 76-93 are not anticipated by the '178 application for the reasons set forth above.

Accordingly, this rejection should be withdrawn.

II. The rejection of claims 26, 28, 61 and 63 under 35 U.S.C. § 102(b)

Claims 26, 28, 61 and 63 have been rejected as anticipated by Ninan, Depression Anxiety 2000;12(Suppl 1):90-94 (abstract) ("Ninan"). According to the examiner, Ninan discloses that venlafaxine, a SNRI, is useful to treat symptoms of fibromyalgia and chronic pain. The Examiner acknowledges that Ninan does not disclose that venlafaxine inhibits NE reuptake to an equal or greater extent than it inhibits the reuptake of serotonin, or that it has NMDA receptor antagonistic properties. The Examiner contends that "a compound that yields the instant method [i.e.,

venlafaxine]" inherently "inhibits NE reuptake to an equal or greater extent than it inhibits the reuptake of serotonin, that it has NMDA receptor antagonistic properties" (Office Action, page 3).

Applicant respectfully requests that this rejection be withdrawn for the following reasons. NMDA receptor antagonism is not an inherent feature of a compound that yields the instant method (see I(B) above). Further, the SNRI compounds venlaxafine and duloxetine do not inhibit NE reuptake to an equal or greater extent than they inhibit the reuptake of serotonin. *See* Vaishnavi, et al., Biol Psychiatry 2004;55:320-322, 320) (venlafaxine and duloxetine preferentially block 5-HT reuptake) (Attached as Exhibit 3). Thus, the preferential inhibition of NE reuptake is not an inherent feature of a compound that yields the instant method.

Milnacipran preferentially blocks the reuptake of NE. *See, e.g.,* specification, page 11, line 5; Vaishnavi, at 320 (Milnacipran's reuptake profile: "is in contrast to those of 5-HT-NE uptake inhibitors (SNRI) (e.g., venlafaxine and duloxetine) where 5-HT uptake is preferentially blocked."). Further, milnacipran has NMDA receptor antagonist properties. *See, e.g.,* specification, page 9, lines 25-26.

Accordingly, this rejection of claims 26, 28, 61 and 63 should be withdrawn, and claims 76-93 are not anticipated by Ninan.

III. The first rejection of claims 61 and 63 under 35 U.S.C. § 102(b)

Claims 61 and 63 have been rejected as anticipated by MEDLINE AN 2001337451, Barkin et al., Am J Therapeutics 2000;7(1):31-47 (abstract) ("Barkin"). According to the Examiner, Barkin discloses that venlafaxine is useful to treat chronic pain. The Examiner acknowledges that Barkin does not disclose that venlafaxine inhibits NE reuptake to an equal or greater extent than it inhibits the reuptake of serotonin, or that it has NMDA receptor antagonistic properties. The Examiner contends that these properties would be inherent in a compound that yields the instant method.

Applicant respectfully requests that this rejection be withdrawn because NMDA receptor antagonistic properties and preferential NE reuptake inhibition are not inherent in a compound that yields the instant method. *See* I(B) and II, above. Further, for the reasons stated above, claims 76-93 are not anticipated by Barkin.

IV. The second rejection of claims 61 and 63 under 35 U.S.C. § 102(b)

Claims 61 and 63 have been rejected as anticipated by MEDLINE AN 97363915, Aronson, Clin Therapeutics 1997;19(3):420-432 (abstract) ("Aronson") and MEDLINE AN 97229930, Lewis et al., Am J Health System Pharmacy 1997;54(6):643-652 (abstract) ("Lewis"). According to the Examiner, Aronson and Lewis disclose that tramadol is an SNRI that is useful to treat chronic pain. Aronson and Lewis do not disclose that tramadol inhibits NE reuptake to an equal or greater extent than it inhibits the reuptake of serotonin or has NMDA receptor antagonistic properties. The Examiner contends that a compound that yields the instant method inherently has these properties.

Applicant requests that this rejection be withdrawn because NMDA receptor antagonistic properties and preferential NE reuptake inhibition are not inherent in a compound that yields the instant method. *See* I(B) and II, above. Further, the specification discloses that a SNRI can be administered adjunctively with *other* active compounds, including tramadol (specification, page 11, lines 5-11). Thus, tramadol is not a SNRI.

Accordingly, this rejection of claims 61 and 63 should be withdrawn, and claims 76-93 are not anticipated by Aronson and Lewis.

V. The rejection of claims 61 and 63 under 35 U.S.C. § 102(a)

Claims 61 and 63 have been rejected as anticipated by MEDLINE AN 2001240387, Enggaard et al., Clin Pharmacol Therapeutics 2001;69(4):245-251 (abstract) ("Enggaard"). According to the Examiner, Enggaard discloses that venlafaxine is a SNRI that is useful to treat symptoms of fibromyalgia and chronic pain. Enggaard does not disclose that venlafaxine inhibits NE reuptake to an equal or greater extent than it inhibits the reuptake of serotonin or has NMDA receptor antagonistic properties. The Examiner contends that a compound that yields the instant method inherently has these properties.

For the reasons stated in I(B) and II, above, the Applicant requests that this rejection of claims 61 and 63 be withdrawn. For these same reasons, claims 76-93 are not anticipated by Enggaard.

VI. The rejection of claims 26, 28-35, 37-43, 45-50, 56, 58-61, 63-66, 68-71, and 73-75 under 35 U.S.C. § 103(a)

Claims 26, 28-35, 37-43, 45-50, 56, 58-61, 63-66, 68-71, and 73-75 have been rejected as obvious over Ninan in view of '178. According to the Examiner, Ninan discloses that venlafaxine, a SNRI, is useful to treat symptoms of fibromyalgia and chronic pain; and '178 discloses a method of using sibutramine to treat pain of CFS and FMS.

The Examiner acknowledges that Ninan does not disclose that venlaxafine: (1) inhibits NE reuptake to an equal or greater extent than it inhibits the reuptake of serotonin, (2) has NMDA receptor antagonistic properties, (3) is administered adjunctively with a second compound, and (4) is formulated in a sustained release dosage formulation. However, the Examiner contends that a compound that yields the instant method inherently inhibits NE reuptake to an equal or greater extent than it inhibits the reuptake of serotonin, and has NMDA receptor antagonist properties (Office Action, page 5).

According to the Examiner "it would be obvious to combine sibutramine with venlaxafine to treat pain or other symptoms of CFS or FMS because "they are both used in the art to ameliorate pain and other symptoms" (*id.*). Further, the Examiner contends that a sustained release formulation would be obvious because such a dosage form is conventional and known in the art.

Applicant respectfully requests that this rejection be withdrawn. Claims 26, 28-35, 37-43, 45-50, 56, 58-61, 63-66, 68-71, and 73-75 are non-obvious over Ninan and '178 because neither reference discloses or suggests: (1) the use of a NE > 5-HT SNRI to treat FMS, pain and CFS; (2) that a SNRI possesses NMDA receptor antagonistic properties, (3) the administration of a NE > 5-HT SNRI adjunctively with a second compound, and (4) a NE > 5-HT SNRI formulated in a sustained release dosage formulation. Further, a SNRI does not inherently inhibit the reuptake of NE to a greater extent than it inhibits the reuptake of serotonin, and a SNRI does not inherently possess NMDA receptor antagonist properties.

Sibutramine is a triple reuptake inhibitor, not a SNRI. *See* I(A), above; Krishnan Declaration, paragraph 12. SNRIs, e.g., venlaxafine, do not inherently inhibit the reuptake of NE to an equal or greater extent than it inhibits the reuptake of 5-HT. *See* II, above; Vaishnavi at 320. A

SNRI does not inherently possess NMDA receptor antagonist properties because at least one SNRI, duloxetine, does not possess these properties. *See* II, above. Because Ninan and '178 do not disclose or suggest a NE > 5-HT SNRI, they do not disclose or suggest the use of such compounds adjunctively with a second compound or in a sustained release formulation. Thus, even if one of ordinary skill in the art was motivated to combine the teachings of these two references, he could not arrive at the instantly claimed methods.

In view of the foregoing arguments, this rejection should be withdrawn. Further, for the reasons set forth above, claims 76-93 are not obvious over Ninan and '178.

VII. The provisional rejection for obviousness-type double-patenting

This rejection is obviated by the attached Terminal Disclaimers, which indicate that the Applicant has a 100% interest in the instant application.

Conclusion

No new matter has been added by these amendments. In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,

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